

96. The pharmaceutical composition of claim 95 wherein the C-terminal amino acid residue of said Substance P receptor binding moiety is Gly-COOEt, Lys-COOEt or Arg-COOEt.
97. The pharmaceutical composition of claim 96 wherein said Substance P receptor binding moiety is a peptide having any one of SEQ ID Nos: 28-30, or a C-terminal fragment or C-terminal derivative thereof.
98. The pharmaceutical composition of claim 62 wherein the opioid receptor binding moiety is endomorphin 1, endomorphin 2, or an N-terminal fragment or N-terminal derivative thereof; and the Substance P receptor binding moiety is Substance P, or a C-terminal fragment or C-terminal derivative thereof.
99. The pharmaceutical composition of claim 62 wherein the peptide has SEQ ID No: 42.
100. The pharmaceutical composition of claim 62 wherein the peptide has SEQ ID No: 43.

12. Please replace claim 102 with amended claim 102:

102. The pharmaceutical composition of claim 62 wherein said peptide comprises at least one D-amino acid.

REMARKS

Claims 1, 2 and 24-102 are currently pending in the subject application. Claims 34-44, 53, 56, 75-85, 94 and 97 have been withdrawn from consideration by the Examiner as being drawn to a non-elected invention (*i.e.*, delta and kappa opioid receptor binding moieties). The Examiner has further withdrawn claims 58, 59, 99 and 100 from consideration based on election by original presentation. The Examiner further rejected claims 1, 2, 24-26, 31, 33, 45-52, 54, 55, 60-67, 72, 74, 86-93, 95, 96, 101 and 102 for encompassing non-elected subject matter. In

addition, claims 1, 2, 24-33, 45-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 stand rejected under 35 U.S.C. § 102, first paragraph, for lack of written description and/or lack of enablement. The Examiner further rejected claims 1, 2, 24-33, 45-49, 50-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 under 35 U.S.C. § 103 (a). Applicant has amended claims 1, 28, 31-33, 45-46, 49, 53, 56-57, 61, 64, 69-74, 86-100 and 102, and has canceled claims 24-27, 34-44, 60, 65-68, 75-85 and 101. However, Applicant explicitly reserves the right to pursue the subject matter any of the canceled claims in continuing or divisional applications. Applicant respectfully submits that amended claims 1, 28, 31-33, 45-46, 49, 53, 56-57, 61, 64, 69-74, 86-100 and 102 are fully supported by the specification and that no new matter is added through these amendments. Below we address each of the rejections stated in the Office Action as if it were applied to the newly amended claims.

Amendment of Claims

Claims 1, 28, 31-33, 45-46, 49, 53, 56-57, 61, 64, 69-74, 86-100 and 102 have been amended, and claims 24-27, 34-44, 60, 65-68, 75-85 and 101 have been canceled. Claims 2, 29, 30, 47, 48, 50-52, 54, 55, 58, 59 and 62-63 remain unchanged. Applicant submits that no new matter is added with these amendments and that support for the newly amended claims can be found in the claims as originally filed and throughout the specification. Specifically, claim 1 has been amended to more particularly claim the chimeric peptides of the invention (e.g., μ opioid receptor binding moiety at N-terminus and agonist Substance P receptor binding moiety at C-terminus), and to recite that the inventive chimeric peptide induces analgesia. Support for such language can be found throughout the specification and in original claim 2.

Claim 28 has been amended to correct claim dependency.

Claims 31-33 have been amended to correct formal matters (e.g., to insert a comma between “fragment and “or”, and to insert “an” between “or and “N-terminal”) and to remove the Markush language. No new matter is added with these amendments.

Claims 45 and 46 have been amended to correct formal matters (*e.g.*, to insert a comma between “fragment and “or”, and to move the term “agonist” in front of the term “Substance P”) and to correct claim dependency. No new matter is added with these amendments.

Claims 49, 53, 56 and 57 no longer include Markush language. In addition, claims 49, 53 and 56 have been amended to correct a clerical error (*i.e.*, to replace the term “N-terminal” with the term “C-terminal”). Claims 49, 53 and 56 relate to the Substance P receptor binding moiety and therefore should refer to C-terminal fragments and/or C-terminal derivatives of SP, as is described throughout the specification and in claim 57.

Claim 61 has been amended to correct claim dependency.

Claims 64, 69-74, 86-100 and 102 have been amended (1) to correct claim dependency, (2) to replace the term “composition” with the term “pharmaceutical composition” and (3) to introduce some of the linguistic changes discussed above with the claims 1, 2, 28-33, 45-59 and 61 (*i.e.*, to incorporate amendments made in the compound claims).

Applicant respectfully submits that the amendments, as described above and detailed herein, does not present new matter, and Applicant thus respectfully requests consideration of these amendments in the following remarks.

Election by Original Presentation

The Examiner states that claims 58, 59, 99 and 100 (SEQ ID No.: 42 and 43) are directed to an invention that is independent and distinct from the originally claimed invention. The Examiner further states that Applicant elected SEQ ID No.: 3 as the opioid receptor binding moiety and SEQ ID No.: 21 as the nociceptive receptor binding moiety. The Examiner asserts that the inventions of the elected group (SEQ ID Nos.: 3 and 21) are distinct from that of a Group drawn to SEQ ID No.: 42 or 43 because they are products which possess characteristic differences in structure and function and each has an independent utility that is distinct for each invention which cannot be exchanged.

The present claims are drawn to chimeric peptides comprising a μ opioid receptor binding moiety at the N-terminus (of which SEQ ID No.: 3 is a species) and an agonist

Substance P receptor binding moiety at the C-terminal (of which SEQ ID No.: 21 is a species). Applicant points out that SEQ ID Nos.: 3 and 21 represent μ opioid receptor and SP receptor binding moieties, respectively; whereas SEQ ID No.: 42 and 43 represent chimeric peptides comprising a μ opioid receptor binding moiety at the N-terminus and a Substance P receptor binding moiety at the C-terminal. In fact, SEQ ID No.: 42 and 43 are chimeric peptides resulting from the fusion of a fragment of the μ opioid receptor binding moiety having SEQ ID No.: 3 with a fragment and/or derivative of the SP receptor binding moiety having SEQ ID No.: 21. Therefore, Applicant asserts that SEQ ID No.: 42 and 43 *do* fall within the scope of the originally claimed invention, and respectfully submits that Applicant is entitled to have claims 58, 59, 99 and 100, and claims dependent thereon, examined on the merits.

Claim Objections

A. The Examiner has objected to claims 1, 2, 24-26, 31, 33, 45-52, 54, 55, 60-67, 72, 74, 86-93, 95, 96, 101 and 102 for encompassing non-elected subject matter (*i.e.*, delta and kappa opioid receptor binding moieties). Applicant notes that claims 34-44 and 75-85 are also drawn to chimeric peptides comprising delta and kappa opioid binding moieties and therefore will address the objection with respect to these claims as well.

Applicant has canceled claims 24-26, 34-44, 65-67 and 75-85 drawn to chimeric peptides comprising delta and kappa opioid binding moieties, therefore the objection is now moot with respect to these claims. In addition, Applicant has amended claims 1 and 62 to recite “wherein said peptide comprises *a μ opioid receptor binding moiety* at its N-terminus”, and has amended claims 44, 46, 86, 87 and 102 so that they now depend on claim 1. Therefore the objection is also moot with respect to claims 1, 2, 45-48, 61-64, 86-89, 101 and 102.

With regard to the Examiner’s statement that the claims recite SEQ ID Nos. other than SEQ ID Nos.: 3 and 21, and that the claims will be examined insofar as they read on the elected subject matter (*i.e.*, SEQ ID Nos: 3 and 21), Applicant notes that, in response to the Restriction Requirement dated December 14, 2000, Applicant elected Group I directed to claims 1-17, drawn to a chimeric peptide in which the opioid receptor binding moiety is a μ opioid receptor

binding moiety, but omitted to elect a species of chimeric peptide, namely one SP receptor binding moiety and one opioid receptor binding moiety. In the Office Action issued July 30, 2001, the Examiner reiterated the species election requirement. Applicant understood that, in that Office Action (*i.e.*, paper No. 8), the Examiner had withdrawn the then pending election of species requirement and had issued a new election of species requirement whereby Applicant was required to elect a single disclosed species of the μ opioid receptor binding moiety (*e.g.*, one of SEQ ID Nos.: 1-11) and a single disclosed species of the SP receptor binding moiety (*e.g.*, one of SEQ ID Nos.: 21-41). Accordingly, in the Response to Requirement for Election of Species filed September 26, 2001, Applicant elected SEQ ID No.: 3 as a single disclosed species of the μ opioid receptor binding moiety and SEQ ID No.: 21 as a single disclosed species of the SP receptor binding moiety, for prosecution on the merits. It is Applicant's understanding that the claims will be restricted to these species if no claim is finally held to be allowable. However, upon allowance of a generic claim, Applicant should be entitled to consideration of claims to additional μ opioid receptor binding moiety species (*i.e.*, SEQ ID Nos.: 1, 2, 4-11) and agonist SP receptor binding moiety species (*i.e.*, SEQ ID Nos.: 25-30, 36 and 38-41). Currently, claims 1-2, 28-30, 45-48, 50-52, 54-55, 61-64, 69-71, 86-89, 91-93, 95-96 and 102, and 57 and 98 in part, are generic.

B. The Examiner has objected to the language of claims 25 and 66, reciting "which ligand". Claims 25 and 66 have been canceled, thereby obviating the objection.

C. The Examiner has objected to claims 28-33, 67 and 69-74 for being dependent from rejected claims 24, 25, 27, 65, 66 or 68. Claim 67 has been canceled and the dependency of claims 28 and 69 has been amended so that these claims, and claims dependent thereon (*i.e.*, claims 29-33 and 70-74), no longer depend on the stated rejected claims, thereby obviating the objection.

D. The Examiner has objected to claims 32, 45, 73 and 86 and states that the syntax could be improved by inserting a comma between the word "fragment" and "or". Applicant has amended the claims as suggested by the Examiner, therefore the objection is now moot.

E. The Examiner has objected to claims 32, 66 and 73 and states that the syntax could be improved by inserting the word “an” between the words “or” and “N-terminal derivative”. Applicant has canceled claim 66 and has amended claims 32 and 73 as suggested by the Examiner, therefore the objection is now moot.

Rejections under 35 U.S.C. § 112, first paragraph - enablement

The Examiner has rejected claims 1, 2, 24-33, 45-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention. Specifically, the Examiner argues that, while the specification is enabling for chimeric peptides comprising an N-terminal opioid receptor binding moiety and a C-terminal agonist Substance P receptor binding moiety wherein the opioid receptor binding moiety is an endogenous μ opioid peptide, or fragment thereof, and the agonist Substance P receptor binding moiety is Substance P, or fragment thereof, it does not reasonably provide enablement for all μ opioid receptor binding moieties, Substance P receptor agonist binding moieties, “*derivatives*” thereof, those which comprise “*at least one non-natural amino acid*”, or “*pharmaceutical compositions*” thereof. The Examiner further argues that Applicant has not provided sufficient guidance or working examples of any μ opioid receptor binding moieties other than those listed in Table 1 being based on the structure of endogenous μ opioid receptor binding moieties, or any SP receptor agonist binding moieties other than those listed in Table 4 of the specification.

Several claims have been canceled and certain claims have been amended, however, the language objected to by the Examiner (e.g., “*derivatives*” and “*pharmaceutical compositions*”) is used in the newly amended claims and thus the appropriateness of this language with respect to the enablement issue will be addressed. Specifically, claims 31-33, 45, 54-57 and 61 (as well as the corresponding composition claims) recite the language said to lack enablement and thus the rejection for lack of enablement under 35 U.S.C. § 112, first paragraph will be addressed as if it were applied to these newly amended claims.

With respect to the expression "at least one non-natural amino acid", Applicant respectfully disagrees that the specification does not provide full support, however, in an effort to expedite prosecution, Applicant has canceled all claims including this language (*i.e.*, claims 60 and 101), thereby obviating the rejection.

Applicant challenges the Examiner's assertion that the specification does not enable any person of ordinary skill in the art to practice the invention using μ opioid receptor binding moieties other than those listed in Table 1, and/or SP receptor agonist binding moieties other than those listed in Table 4 of the specification. The specification makes it abundantly clear that the invention is not restricted to the opioid and SP receptor binding moiety disclosed in the specification (*e.g.*, Tables 1 and 4) for constructing the inventive chimeric peptides. Applicant asserts that it is clear to a person of ordinary skill in the art wishing to practice the invention that other peptidic moieties that interact with a μ opioid receptor (particularly μ opioid receptor agonists) and peptidic moieties that agonize an SP receptor may be used to make the chimeric peptides of the invention. The specification provides sufficient guidance to make and use chimeras including a μ opioid receptor agonist SP receptor binding moieties other than those described in Tables 1 and 4. All that would be required is knowing 1) what sequences might be used, 2) how to determine whether the sequences are desirable for making the inventive chimeras, 3) how to make chimeras and 4) how to establish that the chimeras are analgesic. Applicant asserts that the specification provides ample guidance for 1)-4) above. For example, the specification refers to methods to identify peptides, or variants thereof, that function as agonists (or antagonists) by screening combinatorial libraries of mutants of the parent peptide for peptide agonist (or antagonist) activity (see, for example, pages 9-13 of the specification). In addition, Applicant has provided methods of evaluating the inventive chimeric peptides for analgesic activity (see, for example, pages 22-26 of the specification). Thus, Applicant has not only disclosed chimeric peptides comprising a μ receptor binding moiety at its N-terminus and an agonist SP receptor binding moiety at its C-terminus, but they also have demonstrated that such chimeras *can* be analgesic.

The μ opioid receptor binding moieties and SP receptor binding moieties listed in Tables 1 and 4, respectively, are only representative examples to illustrate how the invention may be practiced. Applicant is not required to disclose every operable species, but only representative examples, with enough teaching and guidance so as to enable a person of ordinary skill in the art to practice the invention without undue experimentation. The specification provides examples of starting materials or precursors suitable to construct the chimeric peptides of the invention (see, for example Table 1-4 on pages 14-17 of the Specification), and also provides ample teaching of potential methods suitable to prepare N-terminal derivatives or fragments, and C-terminal derivatives or fragments of the recited opioid and SP receptor binding moieties, respectively. Applicant asserts that the specification discloses *at least one* method for making and using the claimed invention, which bears a reasonable correlation to the entire scope of the claim. Therefore, the enablement requirement of 35 U.S.C. § 112 is satisfied (*In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); MPEP 2164.01(b)).

With respect to the *Wands* factors, the state of the art in the area of opioid peptides and tachykinin peptides is quite high. The same is true for the field of peptide synthesis, as illustrated by the citations listed on page 5 lines 5-19 of the Specification. One of ordinary skill in the art would be expected to have at least an advanced degree, such as a Ph.D. Applicant asserts that such a person, armed with knowledge provided by the present invention, the cited scientific references, and knowledge available in the art at the time the invention was made, could, without undue experimentation, produce many different chimeric peptides with analgesic properties, and would understand what a peptide derivative is in light of the teachings provided in the specification and in light of common knowledge in the art. Applicant notes that arguments supporting the notion that the use of this term in the specification met the requirement of 35 U.C.C. § 112, first paragraph (enablement) were presented in the Response to Office Action filed March 15, 2002. For the convenience of the Examiner, Applicant has reiterated below arguments presented in the previous Response. Specifically, the term "derivative" is generally defined in the paragraph bridging page 10 and page 11 in the Specification. The specification further recites various methods, known in the art, for preparing peptide derivatives and analogs

suitable for designing opioid receptor and SP receptor binding moieties and for making the inventive chimeric peptides, citing several references (pages 9-13 of the Specification). Furthermore, as noted by the Examiner, the specification describes examples of possible peptide sequence alterations that are included within the meaning of the term “derivative” (see page 11, lines 13-23). Hence, substitutions, additions and/or deletions of amino acid residues, resulting in functionally-equivalent molecules are encompassed within the meaning of the term “derivative”. A person of ordinary skill in the art would understand that the term “functionally-equivalent molecules” refers to molecules (e.g., peptide derivatives) that exhibit the desired function for practicing the present invention, specifically opioid receptor and/or SP receptor binding capability, as it is abundantly described throughout the specification. In addition to the literature cited in the application, Applicant has provided herewith an article from 1995 summarizing structure-activity studies revealing neuropeptide structure characteristics for maintaining functionality (e.g., opioid and SP receptor binding properties). See, Lipkowski *et al.*, “Neuropeptides: Peptide and Nonpeptide Analogs” in *Peptides: Synthesis, Structures and Applications*, B, Gutte, ed., Academic Press, 1995, pp. 287-320, and references cited therein. Thus, a person of ordinary skill in the art, armed with the teachings of the present invention and the knowledge available in the art at the time the invention was made, would not be at a loss and would know how to make chimeric peptides capable of inducing analgesia from derivatives and/or fragments of μ opioid receptor binding moieties and agonist SP receptor binding moieties known in the art, without undue experimentation.

With respect to the term “adjuvant”, Applicant emphasizes that “adjuvant” has no correlation with the common meaning of the term in the field of immunology. The specification makes it abundantly clear that the invention relates to chimeric peptides with *analgesic* properties, useful for the *treatment of pain*. Therefore, the skilled artisan would understand the term “adjuvant” to mean a drug or agent that has a primary indication other than pain but can be analgesic in some conditions, and that is co-administered with an inventive analgesic chimeric peptide to overcome its side effects or boost its analgesic potency, which is the common meaning of the term in the field of analgesia and pain treatment. Applicant has provided herewith a copy

of "Management of Cancer Pain"; Clinical Guideline Number 9; Agency of Health Care Policy and Research (AHCPR) Publication No. 94-0592, March 1994, which was viewed as guidance for medical practice at the time the invention was made, where the term "adjuvant" is defined and examples of adjuvants commonly used in the field are given (see pages 36-38 and Table 14 on pages 185-186). Thus, Applicant submits that the specification provides adequate guidance and teaching of how to use the inventive chimeric peptides in pharmaceutical compositions for inducing analgesia and/or treating pain in a subject.

In summary, Applicant respectfully disagrees that the specification does not reasonably provide enablement commensurate with the scope of the claims, and instead submits that the specification provides sufficient guidance for one of ordinary skill in the art to make and use the invention as claimed without undue experimentation. Specifically, Applicant respectfully submits that the specification *does* provide sufficient guidance and *does* teach one of ordinary skill in the art how to make functional chimeric peptides comprising an opioid receptor binding moiety at its N-terminus and an agonist Substance P (SP) receptor binding moiety at its C-terminus, without undue experimentation. Considering the *Wands* factors--the quantity of experimentation necessary, the amount of direction or guidance present, the presence of working examples, the nature of the invention, the state of the prior art, the predictability of the art, and the breadth of the claims, Applicant submits that the claimed invention is enabled to its present scope and that the claims should not be limited to the μ opioid receptor and SP receptor binding moieties listed in Tables 1 and 4 of the specification, respectively. Therefore, Applicant respectfully requests that the rejection for lack of enablement be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph – written description

The Examiner has rejected claims 25-33, 45-52, 54, 55, 57, 60, 61, 66-74, 86-93, 95, 96, 98, 101 and 102 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner argues that Applicant has only provided adequate written

description regarding endogenous μ opioid receptor binding moieties and endogenous SP receptor binding moieties. The Examiner also asserts that the specification fails to provide a representative number of species to describe the genus of claimed "derivatives".

Applicant challenges the Examiner's assertion that the specification only provides adequate written description regarding endogenous μ opioid receptor binding moieties and endogenous SP receptor binding moieties. The specification makes it abundantly clear that the invention is not restricted to the opioid receptor and SP receptor binding moiety disclosed in the specification (*e.g.*, Tables 1 and 4) for constructing the inventive chimeric peptides. Applicant asserts that it is clear to a person of ordinary skill in the art wishing to practice the invention that other peptidic moieties that interact with a μ opioid receptor (particularly μ opioid receptor agonists) and peptidic moieties that agonize an SP receptor may be used to make the chimeric peptides of the invention. As discussed above, Applicant teaches 1) what sequences might be used, 2) how to determine whether the sequences are desirable for making the inventive chimeras, 3) how to make chimeras and 4) how to establish that the chimeras are analgesic, which is all that is required to practice the present invention. Therefore, the written description requirement is fulfilled.

For example, the specification refers to methods to identify peptides, or variants thereof, that function as agonists (or antagonists) by screening combinatorial libraries of mutants of the parent peptide for peptide agonist (or antagonist) activity (see, for example, pages 9-13 of the specification). In addition, Applicant has provided methods of evaluating the inventive chimeric peptides for analgesic activity (see, for example, pages 22-26 of the specification). The endogenous μ opioid receptor binding moieties and SP receptor binding moieties listed in Tables 1 and 4, respectively, are intended to illustrate, and not limit, the scope of the invention. Other opioid receptor binding moieties and SP receptor binding moieties within the scope of the invention will be apparent to those skilled in the art to which the invention pertains. Applicant reiterates and emphasizes that the examples listed in Tables 1 and 4 of the specification are put forth so as to provide those of ordinary skill in the art with examples of how to make and use the method and products of the invention, and are not intended to limit the scope of what Applicant

regards as their invention. The specification provides examples of starting materials or precursors suitable to construct the chimeric peptides of the invention (see, for example Table 1-4 on pages 14-17 of the Specification), and also provides ample teaching of potential methods suitable to prepare N-terminal derivatives or fragments, and C-terminal derivatives or fragments of the recited opioid and SP receptor binding moieties, respectively.

With respect to the term “derivative”, as discussed above, the term “derivative” is generally defined in the paragraph bridging page 10 and page 11 in the Specification. The specification further recites various methods, known in the art, for preparing peptide derivatives and analogs suitable for designing opioid receptor and SP receptor binding moieties and for making the inventive chimeric peptides, citing several references (pages 9-13 of the Specification). Furthermore, as noted by the Examiner, the specification describes examples of possible peptide sequence alterations that are included within the meaning of the term “derivative” (see page 11, lines 13-23). Hence, substitutions, additions and/or deletions of amino acid residues, resulting in functionally-equivalent molecules are encompassed within the meaning of the term “derivative”. A person of ordinary skill in the art would understand that the term “functionally-equivalent molecules” refers to molecules (e.g., peptide derivatives) that exhibit the desired function for practicing the present invention, specifically opioid receptor and/or SP receptor binding capability, as it is abundantly described throughout the specification. In addition, Applicant refers to the review article by Lipkowski *et al.* (See, Lipkowski *et al.*, “Neuropeptides: Peptide and Nonpeptide Analogs” in *Peptides: Synthesis, Structures and Applications*, B, Gutte, ed., Academic Press, 1995, pp. 287-320, and references cited therein) and asserts that knowledge about designing neuropeptide derivatives that retain the desired functionality (e.g., opioid and SP receptor binding properties) was available at the time the invention was made. Therefore, a person of ordinary skill in the art, armed with the teachings of the present invention and the knowledge available in the art at the time the invention was made, would know how to make chimeric peptides capable of inducing analgesia from derivatives and/or fragments of μ opioid receptor binding moieties and agonist SP receptor binding moieties known in the art.

In view of the foregoing Remarks, Applicant respectfully submits that, as required under 35 U.C.C. § 112, first paragraph, the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed, and thus respectfully requests that the rejection under 35 U.C.C. § 112, first paragraph (written description) be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 1, 2, 24-33, 45-52, 54, 55, 57, 60-74, 86-93, 95, 96, 98, 101 and 102 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A. The Examiner states that claims 1, 25, 31-33, 45, 49, 57, 66, 72-74, 86, 90 and 98 are confusing since the metes and bounds of “N-terminal” and “C-terminal” are not known. Applicant has canceled claims 25 and 66, therefore the rejection is now moot with respect to these claims. Applicant respectfully disagrees that the terms “N-terminal” and “C-terminal” are confusing. However, in order to expedite prosecution, Applicant has amended claims 1 and 62 to recite “... wherein the peptide comprises an opioid receptor binding moiety *at its N-terminus* and an agonist Substance P receptor binding moiety *at its C-terminus*.” Applicant submits that these claims are perfectly clear and unambiguous. With respect to claims 31-33, 45, 49, 57, 72-74, 86, 90 and 98, Applicant points out that the terms “N-terminal” and “C-terminal” are used in conjunction with the terms “fragment” and “derivative”, and submits that the terms “N- (or C-) terminal fragment” and “N- (or C-) terminal derivative” are perfectly clear in light of the specification. For example, the paragraph bridging page 10 and page 11 in the specification reads: “Derivatives, fragments and analogs provided herein are defined as sequences of at least 6 (contiguous) nucleic acids or at least 4 (contiguous) amino acids, a length sufficient to allow for specific hybridization in the case of nucleic acids or for specific recognition of an epitope in the case of amino acids, respectively. Fragments are, at most, one nucleic acid-less or one amino acid-less than the wild type full length sequence. Derivatives and analogs may be full length or

other than full length, if said derivative or analog contains a modified nucleic acid or amino acid, as described *infra*." Furthermore, as noted by the Examiner, the specification describes examples of possible peptide sequence alterations that are included within the meaning of the term "derivative" (see page 11, lines 13-23). Hence, substitutions, additions and/or deletions of amino acid residues, resulting in functionally-equivalent molecules are encompassed within the meaning of the term "derivative". A person of ordinary skill in the art would understand that the term "functionally-equivalent molecules" refers to molecules (*e.g.*, peptide derivatives) that exhibit the desired function for practicing the present invention, specifically opioid receptor and/or SP receptor binding capability, as it is abundantly described throughout the specification. In addition, Applicant asserts that knowledge about designing neuropeptide derivatives that retain the desired functionality (*e.g.*, opioid and SP receptor binding properties) was available at the time the invention was made, as evidenced by the review article by Lipkowski *et al.* (See, Lipkowski *et al.*, "Neuropeptides: Peptide and Nonpeptide Analogs" in *Peptides: Synthesis, Structures and Applications*, B, Gutte, ed., Academic Press, 1995, pp. 287-320) and references cited therein. Therefore, Applicant submits that it is clear to a person of ordinary skill in the art, armed with the teachings of the present invention and the knowledge available in the art at the time the invention was made, how to make chimeric peptides capable of inducing analgesia from derivatives and/or fragments of μ opioid receptor binding moieties and agonist SP receptor binding moieties known in the art. Applicant maintains that, in light of the specification, the terms "N- or C-terminal fragment" and/or "N- or C-terminal derivative" are perfectly clear and not confusing. Applicant respectfully requests that the stated rejection be withdrawn.

B. The Examiner states that claims 1, 45 and 86 are confusing since it is not clear if the binding moiety binds a SP receptor agonist, or if the SP receptor binding moiety is an agonist. Applicant has amended claims 1, 45 and 86 to recite "an agonist Substance P receptor binding moiety". Applicant submits that one of ordinary skill in the art would understand that Applicant means that the Substance P receptor binding moiety is an agonist. Therefore the rejection is now moot.

C. The Examiner states that claims 24, 25, 27, 65, 66 and 68 are confusing since they recite the phrase “the mu receptor”, and suggests that the claims be amended to recite “a mu receptor”. Applicant has canceled claims 24, 25, 27, 65, 66 and 68, thereby obviating the stated rejection.

D. The Examiner has rejected claims 31, 33, 49, 72 and 90 as reciting an improper Markush group. Applicant has amended the rejected claims so that they no longer include Markush language. Therefore the rejection is now moot.

E. The Examiner states that claims 60 and 101 are confusing with respect to the term “non-natural”. Applicant has canceled claims 60 and 101, thereby obviating the rejection.

F. The Examiner states that claim 63 is confusing since the metes and bounds of the term “adjuvant” are not known. Applicant respectfully disagrees that the term “adjuvant” is not clear. As discussed above, the present invention discloses and claims novel *analgesic* chimeric peptides, and thus the term “adjuvant” is relevant to the art of *analgesia*. In the common usage of the term in the field of analgesia and/or pain treatment, “adjuvant” refers to a drug or agent that has a primary indication other than pain but can be analgesic in some conditions, as described on pages 36-38 of the copy of “Management of Cancer Pain”; Clinical Guideline Number 9; Agency of Health Care Policy and Research (AHCPR) Publication No. 94-0592, March 1994, provided herewith, which was regarded as guidance for medical practice at the time the invention was made. Typically, an adjuvant is a non-opioid agent or drug, which is co-administered with an opioid analgesic to overcome its side effects or boost its analgesic potency. Examples of adjuvants are provided in Table 14 on pages 185-186 of the cited document. Applicant asserts that the term “adjuvant” is clear to one of ordinary skill in the art, and respectfully requests that the rejection be withdrawn.

In light of the foregoing remarks, Applicant respectfully submits that the claims, as amended, particularly point out and distinctly claim the subject matter which Applicant regards as the invention, and requests that the rejection under U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 103 (a)

A. The Examiner has rejected claims 1, 2, 24-33, 45-49, 57, 60-74, 86-90, 98, 101 and 102 under 35 U.S.C. § 103 (a) as being unpatentable over Lipkowski *et al.* (*β-Casomorphins and Related Peptides: Recent Developments*, pp 113-118, 1994; “Lipkowski I”), in view of Lipkowski *et al.* (*Life Sci.*, **33**:141-133, 1983; “Lipkowski II”), in further view of Lipkowski *et al.* (*J. Med. Chem.*, **19**:1222-1225, 1986; “Lipkowski III”), in further view of Maszczynska *et al.* (*Let. Pep. Sci.*, **5**:395-398, 1998; “Maszczynska”), and in further view of Smith *et al.* (U.S. Patent No. 6,310,072; “Smith”). Claims 24-27, 60, 65-68 and 101 have been canceled, thereby rendering the rejection under 35 U.S.C. §103 (a) moot with respect to these claims. Claims 1, 28, 31-33, 45-46, 49, 57, 61, 64, 69-74, 86-100 and 102 have been amended, however, in an effort to expedite prosecution, the rejection will be addressed as if it were applied to these newly amended claims.

The legal standard for establishing a *prima facie* case of obviousness requires that the following three criteria be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claimed limitations.

Applicant respectfully disagrees that the claimed invention is obvious over the combination of the cited references, and further submits that the Examiner has applied an improper “obvious to try” rationale to support the stated rejection. Specifically, Applicant submits that claims 1, 2, 28-33, 45-49, 57, 61-64, 69-74, 86-90, 98 and 102 are not obvious over the combination of the Lipkowski I-III, Maszczynska and Smith references.

The Examiner states that Lipkowski I teaches the production of a chimeric peptide comprising the N-terminal fragment of a casomorphin with the C-terminal fragment of a Substance P (SP) *antagonist*. However, the Examiner has conceded that Lipkowski I does not teach a chimera which comprises the N-terminal fragment of an opioid receptor binding moiety (OM) with an SP *agonist*. The Examiner also states that Lipkowski I teaches an SP receptor

agonist binding moiety identical to SEQ ID NO:21 disclosed in the present invention, and that the amidated C-terminal fragment of this SP agonist is biologically active in producing contractions in the guinea pig ileum, citing Figures 1 and 2 of the Lipkowsky I reference.

The Examiner further states that Lipkowsky II teaches chimeras in which the N-terminal part of the SP receptor agonist binding moiety was replaced by an enkephalin opioid receptor binding moiety, which comprises Tyr¹-Phe⁴, and that this peptide demonstrated naloxone-reversible opiate activity in various in vivo tests (Abstract). The Examiner further states that Lipkowsky III teaches that most endogenous opioid peptide analogs, such as endomorphin 1 and endomorphin 2, contain an N-terminal tetrapeptide fragment and that this tetrapeptide, Tyr¹-Phe⁴, is an important requirement for opioid activity, citing the first paragraph of the introduction.

The Examiner also asserts that the skilled artisan would have had a reasonable expectation of success in producing chimeras comprising the N-terminus of an opioid receptor binding moiety and the C-terminus of a SP receptor binding moiety since techniques to produce chimeras were well known and highly successful in the art at the time the invention was made, as evident from the teachings of Lipkowsky I and Lipkowsky II, who teach that such chimeras already exist and that these chimeras are capable of acting via opioid receptor-expressing neurons to potentiate analgesia.

Applicant respectfully disagrees with the Examiner and challenges the assertion that Lipkowsky I and Lipkowsky II teach chimeric peptides comprising an N-terminal opioid receptor binding moiety and a C-terminal SP receptor binding moiety capable of inducing analgesia. While Lipkowsky I teaches a chimeric peptide comprising the N-terminal fragment of a casomorphin (opioid receptor binding moiety) with the C-terminal fragment of a Substance P (SP) antagonist, and that this chimera potentiates analgesia, there is no teaching or suggestion in Lipkowsky I to combine an opioid receptor binding moiety with an SP receptor agonist binding moiety in a single (chimeric) peptide, nor is there a suggestion that such combination would result in a peptide that induces analgesia. With respect to the SP receptor agonist binding moiety having SEQ ID NO:21 disclosed in Lipkowsky I, Applicant notes that the reported biological activity of the amidated C-terminal fragment of this SP agonist is suggestive that it induces pain

(*i.e.*, contractions in the guinea pig ileum) as would be expected for an SP agonist. Furthermore Lipkowski I does not teach nor suggest that this SP agonist be fused with a μ opioid receptor binding moiety to form a chimeric peptide, or that the resulting chimera have analgesic properties.

With respect to the Lipkowski II reference, Applicant submits that it, in fact, *teaches away* from the present invention. Specifically, the Lipkowski II reference provides no evidence suggestive that the peptide induces analgesia. In fact, the study reports that fusing an enkephalin N-terminal active fragment with the C-terminal active fragment of SP resulted in a peptide that not only showed no opiate activity in the guinea pig ileum model, but also *retained SP-like nociceptive activity* (*i.e.*, induces pain). Specifically, the last paragraph on page 143 reads: “When the ET peptide [*e.g.*, enkephalin N-terminal fragment] was fused with the SP C-terminal active part to form the E-P peptide *its opiate activity on GPI was completely abolished* (fig. 2) and *only the SP-spasmogenic effect was observed.*” This observation was later confirmed by Lei *et al.* in *Eur. J. Pharmacol.*, 193(2):209-215, 1991 (a copy of which is provided herewith), where the alleged peptide (designated SPF in the article) was found to induce pain *in vivo* (*e.g.*, i.t. administration of the peptide in mice induced biting and scratching behavior similar to that observed for SP; See page 211, column 1, second paragraph). In light of the foregoing, a person of ordinary skill in the art would not have been motivated to prepare chimeric peptides comprising an N-terminal opioid receptor binding moiety and a C-terminal SP agonist receptor binding moiety useful for inducing analgesia, because there was no reasonable expectation of success that these chimeras would induce analgesia. Rather, a person of ordinary skill in the art would infer from the teachings of Lei *et al.* and Lipkowski II, that such chimera, while potentially exhibiting some opioid receptor activity, would be expected to retain SP-like nociceptive activity and to induce pain *in vivo*.

The Examiner states that Maszczynska teaches that SP is capable of reinforcing spinal morphine analgesia, citing the Abstract and page 396, left column, first full paragraph. The Examiner further states that Maszczynska also teaches that findings of SP reinforcement of

morphine analgesia indicates “the complementarity, and potential value, of further attention to combination pharmacotherapies applying SP and opioids in concert”, citing the Conclusion.

Applicant respectfully submits that Maszczynska does not disclose or teach chimeric peptides as recited in the present claims. Specifically, AA501 consists of the opioid sequence Tyr-(D)Ala-Gly-Phe- covalently linked through a hydrazide bridge to an NK-1 receptor antagonist moiety: N- α -carbobenzoxy-Trp (see end of paragraph bridging column 2 page 395 and column 1 page 396). Applicant respectfully points out that the C-terminal binding moiety in Maszczynska has no sequence identity with Substance P. Furthermore it is an *NK-1 receptor antagonist*, not a Substance P agonist. Applicant further submits that there is no suggestion or teaching in Maszczynska to combine an opioid binding moiety with a Substance P agonist binding moiety within a single peptide. Paragraph 1, column 2 page 398 reads: “On the other hand, concurrent activation of both SP and opioid systems within discrete concentration ranges of pharmacological *agents* reinforces the analgesic potential of morphine.” Clearly, Maszczynska invokes the concurrent use of *at least two* distinct pharmacological entities for inducing analgesia, as it is emphasized throughout the article. Specifically, Maszczynska involves co-administration of AA501 with Substance P as *separate* compounds as a means to activate both receptors for enhanced analgesia (see Figures 1 and 2 on page 397 and paragraph 1, column 1 on page 398). Thus, the concluding remark stating that the research study indicates that “the complementarity, and potential value, of further attention to combination pharmacotherapies applying SP and opioids [either in opposition or] in concert” is to be taken in the context of the article, *i.e.*, co-administration of an agent capable of interacting with an opioid receptor (*e.g.*, AA501) and an agent capable of interacting with the SP receptor (*e.g.*, SP), as *separate* compounds, *not* as components of a chimeric peptide.

The Examiner asserts that Smith teaches the advantage of co-administering opioid binding moieties (*i.e.*, an opioid and an “adjuvant” opioid), citing Figures 2A and 2B of U.S. Patent 6,310,072 . Applicant respectfully disagrees with the Examiner’s definition of the term “adjuvant”. As discussed above, in the common use of the term, “adjuvant” refers to any drug or agent that has a primary indication other than pain but can be analgesic in some conditions. An

adjuvant is typically a non-opioid agent which is co-administered with an opioid analgesic to overcome side effects or boost the analgesic potency of the primary opioid analgesic. Smith teaches co-administration of *two opioid agonists* for producing analgesic synergy, therefore the Examiner's assertion that Smith teaches the advantage of co-administering an opioid and an "adjuvant" is incorrect. Furthermore, Smith does not teach chimeric peptides and is not relevant to the present invention. In addition, even if Smith taught co-administration of an opioid with an adjuvant, as it is understood within the common usage of the term in the field of analgesia and/or pain treatment, it would not render the present invention obvious in view of Lipkowski I-III and Maszczynska, since there is no suggestion or motivation to combine the teachings of the cited references to achieve the present invention, and the combination of the cited references does not include all of the claim limitations (*e.g.*, (1) a chimeric peptide which induces analgesia comprising (2) an opioid receptor binding moiety at its N-terminus and (3) an agonist SP binding moiety at its C-terminus).

In summary, Applicant respectfully submits that a person of ordinary skill in the art would *not* have found "obvious to try" to combine the teachings of Lipkowski I, Lipkowski II, Lipkowski III, Maszczynska and Smith, because there was no suggestion to combine the references, nor was there any reasonable expectation of success in the combination in order to achieve the claimed invention. Specifically, there is no reasonable expectation of success that a chimeric peptide comprising an opioid receptor binding moiety at its terminus and an agonist SP binding moiety at its C-terminus would bind to both the opioid and SP receptors, and induce analgesia. Applicant emphasizes that the teaching or suggestion to make the claimed combination and the reasonable expectation of success *must both be found in the prior art* and *cannot* be based on Applicant's disclosure (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir, 1991); MPEP 706.02(j)). In addition, as discussed above, the claims, as amended, cannot be obvious over the combination of the cited references because the combination does not teach all of the claim limitations.

Since there is no suggestion or motivation to combine the teachings of Lipkowski I, Lipkowski II, Lipkowski III, Maszczynska and Smith and there is no reasonable expectation of

success in the combination to achieve the claimed invention, and since the references do not teach all of the claim limitations, the claims as set forth in the present response cannot be obvious over the combination of cited references.

B. The Examiner has rejected claims 50-52, 54, 55, 91-93, 95 and 96 under 35 U.S.C. § 103 (a) as being unpatentable over Lipkowski *et al.* (*β-Casomorphins and Related Peptides: Recent Developments*, pp 113-118, 1994; “Lipkowski I”), in view of Lipkowski *et al.* (*J. Med. Life Sci.*, **33**:141-133, 1983; “Lipkowski II”), in further view of Lipkowski *et al.* (*J. Med. Chem.*, **19**:1222-1225, 1986; “Lipkowski III”), in further view of Maszczynska *et al.* (*Lett. Pep. Sci.*, **5**:395-398, 1998; “Maszczynska”) and in further view of Watson *et al.* (*Eur. J. Pharmacol.*, **87**(1):77-84, 1983; “Watson”).

The Examiner states that Watson teaches that C-terminal alkyl esters of SP exhibit a higher degree of selectivity to a particular SP receptor subtype (citing the Abstract and Tables I and II), and asserts that the teachings of Watson would lead one of ordinary skill in the art to make the claimed structures in view of the teachings of Lipkowski I-III and Maszczynska.

Applicant points out that Watson does not teach chimeric peptides, and asserts that there is no teaching or suggestion to use the C-terminal alkyl esters of SP described in Watson for making the chimeric peptides of the invention. Applicant respectfully submits that a person of ordinary skill in the art would *not* have found it “obvious to try” to combine the teachings of Lipkowski I, Lipkowski II, Lipkowski III, Maszczynska and Watson. In addition, there was no suggestion to combine the references, nor was there any reasonable expectation of success in the combination in order to achieve the claimed invention, for the reasons discussed above.

Since there is no suggestion or motivation to combine the teachings of Lipkowski I, Lipkowski II, Lipkowski III, Maszczynska and Watson and there is no reasonable expectation of success in the combination to achieve the claimed invention, and since the references do not teach all of the claim limitations, the claims as set forth in the present response cannot be obvious over the combination of the cited references.

In view of the foregoing Remarks, Applicant respectfully requests that the stated obviousness rejections under 35 U.S.C. § 103 (a) be withdrawn.

Conclusion

In view of the foregoing Amendments and Remarks, Applicant respectfully submits that the present case is now in condition for allowance; a Notice to that effect is hereby requested. Applicant would like to thank the Examiner for careful review and consideration of this case and if the Examiner believes that a telephone interview would be of assistance in advancing the prosecution of this application, the Examiner is invited to telephone the undersigned (617) 248-5150.

Although it is believed that there is no fee associated with this Response, if Applicant is mistaken, please charge any fees to our Deposit Account No.: 03-1721.

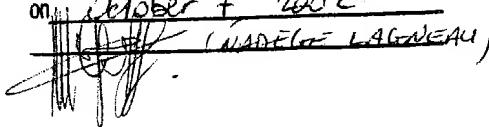
Respectfully submitted,



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I hereby certify this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner For Patents, Washington, D.C. 20231
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